



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY  
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS  
REGISTRATION DIVISION (7505P)

January 27, 2012

**MEMORANDUM:** Companion Animal Safety Studies for 11556-RLL (FLUMETHRIN COLLAR)

Subject: Name of Pesticide Product: PNR1427 INSECTICIDE  
EPA Reg. No. /File Symbol: 11556-RLL  
DP Barcode: DP 385560 + DP 396978  
Decision No.: 440307  
Action Code: R110.0  
PC Codes: 129099 (Imidacloprid)  
036007 (Flumethrin)

From: Byron T. Backus, Ph.D., Toxicologist  
Technical Review Branch  
Registration Division (7505P)

*Byron T. Backus*  
*Jan. 27, 2012*  
*W. Ashi*

To: BeWanda Alexander/Richard Gebken RM 10  
Insecticide Branch  
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

**FORMULATION FROM LABEL:**

<u>Active Ingredient(s):</u>	<u>by wt.</u>
129099 Imidacloprid	10.0%
036007 Flumethrin	4.5%
<u>Other Ingredient(s):</u>	<u>85.5%</u>
TOTAL	100.0%

**ACTION REQUESTED:** The Risk Manager requests:

For DP 385560: "Please review attached companion animal safety studies submitted in support of a new end use product containing two active ingredients: one currently registered (imidacloprid) and a new active ingredient (flumethrin).

For DP 396978: "Please review attached requested companion animal safety studies on adult cats and adult dogs per teleconference on October 20, 2011. Bayer has recalculated the exposure of the target

[companion] animals to the levels of the two active ingredients released from the collars worn by the pets during the study.

## **BACKGROUND:**

The material for review in DP 385560 consists of eight companion animal safety studies for collars (containing 10% imidacloprid and 4.5% flumethrin), as follows: MRID 48240108 (61-day adult cat study); 048240109 (61-day adult dog study); 48240110 (180-day beagle puppy study starting when puppies were 7 weeks old); 48240111 (180-day kitten study starting when kittens were ~10 weeks old); 48240112 (safety of collar + reflectors in puppies); 48240113 (safety of collar + reflectors in kittens); 48240114 (safety of collar ± reflectors in adult cats); and 48240115 (safety of collars ± reflectors in adult dogs).

The material for review in DP 396978 consists of two final report amendments relating to the rate of release of the actives from the collar: MRID 48674701 (Final Report Amendment 1 to the study in MRID 48240109) and 48674702 (Final Report Amendment 2 to the study in MRID 48240108). These two reports were reviewed by TRB and the reviews were incorporated into the DERs for MRIDs 48240109 and 48240108, respectively.

## **COMMENTS AND RECOMMENDATIONS:**

1. A contractor (Summitec Corporation) did the primary reviews on the eight companion animal safety studies and produced a DER for each study; TRB secondarily reviewed the studies and DERs, making revisions where appropriate. The two reports in MRIDs 48674701 and 4867402 were reviewed by TRB, and the reviews were incorporated into the final DERs for MRIDs 48240109 and 48240108, respectively.
2. The studies in MRIDs 48240108 (with the report amendment in 48674702), 48240109 (with the report amendment in 48674701), 48240110 and 48240111 have all been classified as acceptable guideline studies. These studies support the proposed use of this collar in adult dogs and puppies of seven weeks of age and older, and in adult cats and kittens of 10 weeks of age and older.
3. The studies in MRIDs 48240112, 48240113, 48240114 and 48240115 have all been classified as acceptable non-guideline studies. These studies demonstrate that there is no indication of a decrease in safety (or increase in toxicological hazard to the companion animals) associated with the wearing of collars with reflectors.
4. Refer to the attached DERs for the executive summaries and additional comments.

DATA EVALUATION RECORD

CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427 INSECTICIDE COLLAR]

STUDY TYPE: COMPANION ANIMAL SAFETY - CATS (OPPTS 870.7200)

MRID 48240108

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
Arlington, VA 22202

Prepared by  
Summitec Corporation  
9724 Kingston Pike, Suite 602  
Knoxville, Tennessee 37922

Task Order No. 3-C-04

Primary Reviewer:  
Virginia A. Dobozy, V.M.D., M.P.H.

Signature: \_\_\_\_\_  
Date: \_\_\_\_\_

Virginia A. Dobozy, AE  
SEP 27 2011

Secondary Reviewer:  
Donna L. Fefee, D.V.M.

Signature: \_\_\_\_\_  
Date: \_\_\_\_\_

Donna L. Fefee, AE  
SEP 27 2011

Robert Ross, M.S., Program Manager

Signature: \_\_\_\_\_  
Date: \_\_\_\_\_

Robert H. Ross  
SEP 27 2011

Quality Assurance:  
Angie Edmonds, B.S.

Signature: \_\_\_\_\_  
Date: \_\_\_\_\_

Angie Edmonds  
SEP 27 2011

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M  
Technical Review Branch, Registration Division (7505P)

Signature: M. Hashim  
Date: 1-31-12

Template version 02/06

### DATA EVALUATION RECORD

**STUDY TYPE:** Companion Animal Safety Study - Cats; OPPTS 870.7200

**PC CODES:** 129099 (Imidacloprid), 036007 (Flumethrin)

**DP BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR 1427 Insecticide Collar [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)]

**TRADE NAME:** Not provided

**CITATIONS:** Madsen, T.J. (2010) Safety of PNR 1427 in adult cats. Sinclair Research Center, Auxvasse, MO. In-Life Testing Facility Study No. S10065, April 1, 2010. MRID 48240108. Unpublished.

Madsen, T.J. (2010) Final report amendment 1 to SRC study S10065. Sinclair Research Center, Auxvasse, MO. In-Life Testing Facility Study No. S10065, June 2, 2010. MRID 48240108. Unpublished.

Chopade, H. (2011) Final Report Amendment 2 to Bayer Report 33800 (MRID 48240108) - Safety of PNR 1427 in Adult Cats. Project Number: 33968, S10065, 152/152. November 22, 2011. MRID 48674702. Unpublished.

**SPONSOR:** Bayer HealthCare LLC/Animal Health Division, Shawnee Mission, KS

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 48240108), the safety of PNR 1427 insecticide collars containing imidacloprid (10% w/w) and flumethrin (4.5% w/w) was tested in adult domestic short hair cats (9.5 to 9.7 months of age). One group of three male and three female cats served as negative control. Another group of three male and three female cats served as a placebo control and wore five end-use collars minus the active ingredients for 61 days continuously. A third group (1x) of three male and three female cats wore one end-use collar for 61 days continuously. In a fourth group (5x) of six male and six female cats, five end-use collars were applied on day 0 and then replaced with five new collars on days 14, 28 and 42 and removed on day 61. In addition to measuring the required parameters, the end-use collars worn by selected cats in the 1x and 5x groups were analyzed post-removal to determine the exposures of cats to the active ingredients.

All animals survived to the end of the study. Clinical observations reported included mild signs of abnormal feces (loose stool and/or diarrhea), emesis and ocular discharge in all treatment groups; however, no raw or summarized data were included in the final report. No effects on body weight, body weight gain, food consumption or clinical pathology parameters were observed. Statistically

significant findings for hematology and clinical chemistry parameters were not considered treatment-related since they were either isolated, inconsistent or not associated with clinical signs. Based on the chemical analyses of worn collars and additional information reported in MRID 48674702, cats in the 5x group were exposed to 5.2x the dose of imidacloprid and 4.0 x the dose of flumethrin received by cats in the 1x group.

**It is concluded that the margin of safety in adult cats exposed to PNR 1427 insecticide [imidacloprid (10% w/w) + flumethrin (4.5% w/w)] collar for 61 days is 4x based on the chemical analyses of the worn collars which yielded 5.2x the recommended dose of imidacloprid and 4.0x the recommended dose of flumethrin. The mean collar weight (after trimming) applied to the 1x cats was 11.17 g equivalent to 2.82 g/kg body weight.**

This companion animal safety study in male and female adult cats is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the cat. Minor study deficiencies are listed under Section III.C. Deficiencies of this review.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## **I. MATERIALS AND METHODS**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# **Ex. 4 CBI**



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# Ex. 4 CBI

## III. DISCUSSION AND CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that no adverse treatment-related findings were observed in male or female adult cats treated continuously for 61 days, either with zero, one or five PNR 1427 collars or with five placebo collars. Mild thinning of hair, presumed to be induced by mechanical irritation associated with multiple collars, was observed in the throat region of three Group IV (5x end-use product) cats. However, these local changes normalized within 7 days following replacement of the 5-collar set with a single (1) end-use product collar.
- B. **REVIEWER COMMENTS:** A proposed study protocol (MRID 47776601) was reviewed by the Registration Division, OPP, in a Memorandum dated August 26, 2009 (Decision No. 415122). The Agency agreed that three males and three females in the negative and placebo control groups and the 1x group, as opposed to six males and six females per group required by the OPPTS 870.7200 Guideline, were sufficient. The Agency also agreed to the elimination of the 3x group,

which is provided for in the OPPTS 870.200 Guideline as long as there is no evidence of toxicity at 5x the recommended dose.

There were numerous amendments to the protocol after the Agency review.

**Ex. 4 CBI**

## **Ex. 4 CBI**

**Ex. 4 CBI**

The amendment states that this arrangement was approved by Dr. Byron Backus (the EPA reviewer) in a teleconference on September 2, 2009.

All animals survived to the end of the study. Clinical observations reported included mild signs of abnormal feces (loose stool and/or diarrhea), emesis and ocular discharge in all treatment groups; however, no raw or summarized data were included in the final report. No effects on body weight, body weight gain, food consumption or clinical pathology parameters were observed. Statistically significant findings for hematology and clinical chemistry parameters were not considered treatment-related since they were either isolated, inconsistent or not associated with clinical signs. Based on chemical analyses of the worn collars and information reported in MRID 48674702, cats in the 5x group were exposed to 5.2x the recommended dose of imidacloprid and 4.0x the recommended dose of flumethrin.

**It is concluded that the margin of safety in adult cats exposed to PNR 1427 insecticide [imidacloprid (10% w/w) + flumethrin (4.5% w/w)] collar for 61 days is 1x based on the chemical analyses of the worn collars which yielded 5.2x the recommended dose of imidacloprid and 4.0x the recommended dose of flumethrin. The mean collar weight (after trimming) applied to the 1x cats was 11.17 g equivalent to 2.82 g/kg body weight.**

This companion animal safety study in male and female adult cats is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the cat.

### **C. MINOR STUDY DEFICIENCIES:**

## **Ex. 4 CBI**

# Ex. 4 CBI

The deficiencies indicated above are considered to be minor, and do not affect the acceptable classification of this study.

DATA EVALUATION RECORD

CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427, IMIDACLOPRID (10%, W/W) + FLUMETHRIN (4.5%, W/W) COLLAR]

OPPTS 870.7200  
STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- ADULT DOGS  
MRID 48240109

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
Arlington, VA 22202

Prepared by  
Summitec Corporation  
9724 Kingston Pike, Suite 602  
Knoxville, Tennessee 37922

Task Order No. 3-C-04

Primary Reviewer:

Donna L. Fefe, D.V.M.

Signature:

Date:

Donna L. Fefe, AE  
SEP 27 2011

Secondary Reviewers:

Thomas C. Marshall, Ph.D., D.A.B.T.

Signature:

Date:

Thomas C. Marshall, AE  
SEP 27 2011

Robert H. Ross, M.S., Group Leader

Signature:

Date:

Robert H. Ross  
SEP 27 2011

Quality Assurance:

Jennifer Goldberg, B.S.

Signature:

Date:

Jennifer Goldberg  
SEP 27 2011

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EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M  
Technical Review Branch, Registration Division (7505P)

Signature: M. Hashim  
Date: 1-31-12

Template version 02/06

**DATA EVALUATION RECORD**

**STUDY TYPE:** Companion Animal Safety Study - Adult Dogs; OPPTS 870.7200

**PC CODES:** 129099 (Imidacloprid), 036007 (Flumethrin)

**DP BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)]  
Collar (9.96% Imidacloprid and 4.35% Flumethrin; Lot No. KP05KF6)

**SYNONYMS:** M915 Insecticide Animal Collar (large collar)

**CITATIONS:** Madsen, T. (2010) Safety of PNR 1427 in adult dogs. Sinclair Research Center, LLC (SRC), Auxvasse, Missouri. Study Number S10064, April 23, 2010. MRID 48240109. Unpublished.

Chopade, H. (2011) Final Report Amendment 1 to Bayer Report 33805 (MRID 48240109) - Safety of PNR 1427 in Adult Dogs. Sinclair Research Center, Inc. Project Number: 33967, S10064, 152/151. Final Report Amendment 1: November 22, 2011. MRID 48674701. Unpublished.

**SPONSOR:** Bayer HealthCare LLC, Animal Health Division, 12809 Shawnee Mission Parkway, Shawnee Mission, Kansas.

**EXECUTIVE SUMMARY:** In a 61-day companion animal safety study (MRID 48240109), groups of adult male and female beagle dogs were treated with PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars (9.96% Imidacloprid and 4.35% Flumethrin; Lot No. KP05KF6) at 1X (one collar; applied to 3 animals/sex) or 5X (five collars; applied to six animals/sex) the intended label use rate for dogs weighing greater than 8 kg. Two additional groups of three males and three females were untreated or treated with five "Placebo Collars." The multiple collars applied to the placebo controls and 5X animals were affixed around the neck in a "3 x 2" bi-layer arrangement such that a single layer of three collars was in contact with the dog's neck, while a second tier of two collars encircled and directly contacted the foundation layer, and the multiple collars were banded together with nylon cable (zip) ties. Initial treatment was on day 0, and the 5X animals were re-treated on days 14, 28 and 42.

There were no treatment-related effects on mortality, systemic clinical signs, body weight or body weight gain, food consumption, hematology, clinical chemistry, or coagulation parameters. Reversible, treatment-related abnormal local findings such as erythema and hair loss or thinning of the hair on the throat, back of the neck, or side of the neck were noted on two placebo control, two 1X, and five 5X dogs at one or more observations during the treatment interval.



Based on the information in MRID 48674701, the dogs in the 1X and 5X groups were respectively exposed to **Ex. 4 CBI** mg/kg bw and **Ex. 4 CBI** mg/kg bw of imidacloprid and **Ex. 4 CBI** mg/kg bw and **Ex. 4 CBI** mg/kg bw of flumethrin, i.e. the average imidacloprid exposure of the 5X animals was 10.88X that of the dogs in the 1X group, and the average flumethrin exposure of the 5X was 4.05X that of the dogs in the 1X group.

The margin of safety in 8.67 to 13.44-kg adult beagle dogs treated with PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars for 61 days is 4.05X the recommended dose of one collar per dog. The mean collar weight for the 1X dogs was 37.93 grams or 3.22 grams/kg b.w.

It is concluded that this companion animal safety study in dogs is **Acceptable/Guideline** and does satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in adult dogs.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

**Ex. 4 CBI**

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# Ex. 4 CBI

## III. DISCUSSION and CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** According to the study author, no adverse treatment-related findings were observed in male or female adult dogs treated continuously for 61 days either with zero, one, or five PNR 1427 collars or with five placebo collars. The study author stated that mild thinning of the hair under or adjacent to the collars, which was presumed to be related to mechanical irritation from the collars, was noted on dogs in the treated groups (two placebo controls, two 1X animals, and five 5X animals). These changes began to reverse in one placebo control and all 5X animals within 28 days of wearing a single placebo or end-use collar, and the remaining placebo control and 1X animal showed unequivocal hair regrowth after an additional week spent without wearing any collar. The study author concluded that continuous treatment of adult dogs at 5X the recommended label dose for 61 consecutive days was determined to be safe.
- B. **REVIEWER COMMENTS:** The reviewer is in agreement with the study author that there was no indication of systemic toxicity. Reversible local effects under or adjacent to the collars most likely were related to mechanical irritation.

Based on the information in MRID 48674701, the dogs in the 1X and 5X groups were respectively exposed to [Ex. 4 CBI] mg/kg bw and [Ex. 4 CBI] mg/kg bw of imidacloprid and [Ex. 4 CBI] mg/kg bw and [Ex. 4 CBI] mg/kg bw of flumethrin, i.e. the average imidacloprid exposure of the 5X animals was 10.88X that of the dogs in the 1X group, and the average flumethrin exposure of the 5X was 4.05X that of the dogs in the 1X group.

The margin of safety in 8.67 to 13.44-kg adult beagle dogs treated with PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars for 61 days is 4.05X the recommended dose of one collar per dog. The mean collar weight for the 1X dogs was 37.93 grams or 3.22 grams/kg b.w.

It is concluded that this companion animal safety study in dogs is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in adult dogs.

**C. STUDY DEFICIENCIES:**

Deficiencies included the following:

**Ex. 4 CBI**

The deficiencies indicated above are considered to be minor, and do not affect the acceptable classification of this study.

**DATA EVALUATION RECORD**

**CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427, IMIDACLOPRID (10%, W/W) + FLUMETHRIN (4.5%, W/W) COLLAR]**

**OPPTS 870.7200  
STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- PUPPIES  
MRID 48240110**

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
Arlington, VA 22202

Prepared by  
Summitec Corporation  
9724 Kingston Pike, Suite 602  
Knoxville, Tennessee 37922

Task Order No. 3-C-04

Primary Reviewer:

Donna L. Fefee, D.V.M.

Signature:

Date:

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SEP 27 2011

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Robert H. Ross, M.S., Group Leader

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Date:

Robert H. Ross  
SEP 27 2011

Quality Assurance:

Jennifer Goldberg, B.S.

Signature:

Date:

Jennifer Goldberg  
SEP 27 2011

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EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M  
Technical Review Branch, Registration Division (7505P)

Signature: M. Hashim 1/31/12  
Date: 1/31/12

Template version 02/06

**DATA EVALUATION RECORD**

**STUDY TYPE:** Companion Animal Safety Study - Puppies; OPPTS 870.7200

**PC CODES:** 129099 (Imidacloprid), 036007 (Flumethrin)

**DP BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)]  
Collar (Small collars: Lot No. KP05KTJ, 10.18% imidacloprid and 4.47% flumethrin; Large collars:  
Lot No. KP05KF6, 9.96% Imidacloprid and 4.35% Flumethrin)

**SYNONYMS:** M915 Insecticide Animal Collar (large collar and small collar)

**CITATIONS:** Madsen, T. (2010) Safety of PNR1427 in puppies. Sinclair Research Center, LLC  
(SRC), Auxvasse, Missouri. Study Number S10062, June 16, 2010. MRID  
48240110. Unpublished.

**SPONSOR:** Bayer HealthCare LLC, Animal Health Division, 12809 Shawnee Mission Parkway,  
Shawnee Mission, Kansas.

**EXECUTIVE SUMMARY:** In a 180-day companion animal safety study (MRID 48240110),  
groups of six male and six female 7-week-old beagle puppies were treated with PNR 1427  
[Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars (9.96% Imidacloprid and 4.35%  
Flumethrin; Lot No. KP05KF6) at 1X (one collar), 3X (three collars), or 5X (five collars) the  
intended label use rate. Two additional groups of three males and three females were untreated or  
were treated with five "Placebo Collars." The multiple collars applied to the placebo controls and 5X  
animals were affixed around the neck in a "3 x 2" bi-layer arrangement such that a single layer of  
three collars was in contact with the dog's neck, while a second tier of two collars encircled and  
directly contacted the foundation layer, and the multiple collars were banded together with nylon  
cable (zip) ties. Initial treatment was on day 0, and the animals were re-treated (existing collars  
replaced with new collars) on days 29, 90, 125, and 148.

There were no treatment-related effects on mortality, absolute body weight, food consumption,  
hematology or clinical chemistry. The 5X females had a transient decrease in body weight gain (25%  
less than controls during days -1 through 17). Reversible abnormal local findings such as erythema,  
hair loss or thinning of the hair, bruising, abrasions, scabbing, or a part in the hair were noted on two  
negative controls, five placebo controls, nine 1X animals, eight 3X animals, and ten 5X animals at one  
or more observations during the treatment interval. Mildly increased creatine kinase activity in 3X  
and 5X animals (349, 940, 1074 U/L for negative controls, 3X, and 5X, respectively) is of  
undetermined significance.

Based on determination of the collar weight losses and chemical analyses of the worm collars, the  
imidacloprid exposure of puppies in the 3X and 5X groups was 3.02X and 4.89X that of the puppies

in the 1X group, and the flumethrin exposure of puppies in the 3X and 5X groups was 2.46X and 1.45X that of the puppies in the 1X group.

**Based on transient decreased body weight gain, it is concluded that the margin of safety in 7-week-old 1.53- to 2.96-kg beagle puppies treated with PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars is 3X the recommended dose (of one collar per puppy). The average collar dosage rate for 1X animals on Day 0 was 10.156 g, equivalent to 5.096 g/kg.**

This companion animal safety study in puppies is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in juvenile dogs. However it must be noted that, although the puppies in the 5X group were exposed to 4.89X the recommended dose of imidacloprid, the chemical analyses of the worn collars indicates they were exposed to only 1.45X the recommended dose of flumethrin.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

# **Ex. 4 CBI**

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# Ex. 4 CBI

## III. DISCUSSION and CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** According to the study author, no adverse treatment-related findings were observed in male or female puppies treated continuously for 180 days either with zero, one, three, or five PNR 1427 collars or with five placebo collars. The study author stated that mild thinning of the hair in the throat region under or adjacent to the collars was presumed to be related to mechanical irritation from wearing multiple collars. The study author concluded that continuous treatment of puppies at 1X, 3X, and 5X the recommended label dose for 180 consecutive days was well tolerated and determined to be safe.
- B. **REVIEWER COMMENTS:** In disagreement with the study author, toxicity was evident at 5X as a transient decrease in body weight gain in females following the initial treatment on day 0. Elevated CK activity on day 120 in 3x and 5x animals is of undetermined significance.

Based on determination of the collar weight losses and chemical analyses of the worn collars, the imidacloprid exposure of puppies in the 3X and 5X groups was 3.02X and 4.89X that of the puppies in the 1X group, and the flumethrin exposure of puppies in the 3X and 5X groups was 2.46X and 1.45X that of the puppies in the 1X group. During two of the retreatment intervals, the Flumethrin amounts (mg) remaining in the sets of collars exceeded the amounts initially present. This may be due to a problem with the analytical method, a manufacturing problem, or a problem with the study design. It is possible that the 3 x 2 bi-layer arrangement of the collars and/or the use of zip ties to band the collars together inhibited the release of flumethrin from the collars.

Based on transient decreased body weight gain, it is concluded that the margin of safety in 7-week-old 1.53- to 2.96-kg beagle puppies treated with PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars is 3X the recommended dose (of one collar per puppy). The average collar dosage rate for 1X animals on Day 0 was 10.156 g, equivalent to 5.096 g/kg.

- C. **STUDY DEFICIENCIES:** The following deficiencies were identified:

# Ex. 4 CBI

# Ex. 4 CBI

The deficiencies indicated above are considered to be minor, and do not affect the acceptable classification of this study.

DATA EVALUATION RECORD

CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427 INSECTICIDE COLLAR]

STUDY TYPE: COMPANION ANIMAL SAFETY – KITTENS (OPPTS 870.7200)

MRID 48240111

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
Arlington, VA 22202

Prepared by  
Summitec Corporation  
9724 Kingston Pike, Suite 602  
Knoxville, Tennessee 37922

Task Order No. 3-C-04

Primary Reviewer:

Virginia A. Dobozy, V.M.D., M.P.H.

Signature:

Date:

Virginia A. Dobozy, AE  
SEP 27 2011

Secondary Reviewer:

Donna L. Fefee, D.V.M.

Signature:

Date:

Donna L. Fefee, AE  
SEP 27 2011

Robert Ross, M.S., Program Manager

Signature:

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Robert H. Ross  
SEP 27 2011

Quality Assurance:

Angie Edmonds, B.S.

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Date:

Angie Edmonds  
SEP 27 2011

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M.  
Technical Review Branch, Registration Division (7505P)

Signature: M. Hashim  
Date: 4/31/12  
Template version 02/06

### DATA EVALUATION RECORD

**STUDY TYPE:** Companion Animal Safety Study - Kittens; OPPTS 870.7200

**PC CODE:** 129099 (Imidacloprid), 036007 (Flumethrin)

**BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR 1427 Insecticide Collar [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)]

**TRADE NAME:** Not provided

**CITATIONS:** Madsen, T.J. (2010) Safety of PNR 1427 in kittens. Sinclair Research Center, Auxvasse, MO. In-Life Testing Facility Study No. S10063, June 16, 2010. MRID 48240111. Unpublished.

**SPONSOR:** Bayer HealthCare LLC/Animal Health Division, Shawnee Mission, KS

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 48240111), the safety of PNR 1427 insecticide collars containing imidacloprid (10% w/w) and flumethrin (4.5% w/w) was tested in domestic short hair kittens (68 to 71 days old at initiation of treatment). One group of three male and three female kittens served as negative control. Another group of three male and three female kittens served as a placebo control and wore five end-use collars minus the active ingredients for 180 days continuously. In a third group (1x) of six male and six female kittens, one end-use collar was applied on day 0 and then replaced with new collars on days 29, 90 and 149 and removed on day 180. In a fourth group (3x) of six male and six female kittens, three end-use collars were applied on day 0 and then replaced with three new collars on days 29, 90 and 149 and removed on day 180. In a fifth group (5x) of six male and six females kittens, five end-use collars were applied on day 0 and then replaced with five new collars on days 29, 90 and 180 and removed on day 180. In addition to measuring the required parameters, the end-use collars worn by selected kittens in the 1x, 3x and 5x groups were analyzed post-removal to determine the exposures of the kittens to the active ingredients.

All animals survived to the end of the study. Clinical observations reported included mild signs of abnormal feces (loose stool and/or diarrhea), emesis and ocular discharge in all treatment groups; however, no raw or summarized data were included in the final report. No effects on body weight, food consumption or clinical pathology parameters were observed. Statistically significant findings for hematology and clinical chemistry parameters were not considered treatment-related since they were either isolated, inconsistent or not associated with clinical signs. Body weight gain over the course of the study (days -1 to 180) was decreased 17% in the 5x group females, as compared to the

placebo control group. Based on chemical analyses of the worn collars, kittens in the 3x and 5x groups were exposed to 3.59x and 3.13x the imidacloprid exposure, respectively, received by kittens that wore one end-use collar. The kittens in the 3x and 5x groups were exposed to 5.09x and 5.57x the flumethrin exposure, respectively, received by kittens that wore one end-use collar.

**It is concluded that the margin of safety in kittens exposed to PNR 1427 [imidacloprid (10% w/w) + flumethrin (4.5% w/w)] insecticide collar for 180 days is 3x the recommended dose based on decreased body weight gain over the course of the study (days -1 to 180) in females at 5x the recommended dose. In addition, the exposure from the 5x treatment was 5.57x the recommended dose of flumethrin but only 3.13x the recommended dose of imidacloprid, based on the chemical analyses of the worn collars. The average collar dosage rate for 1X kittens on Day 0 was 9.387 g, equivalent to 4.15 g/kg body weight.**

This companion animal safety study in male and female kittens is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the kitten. However it must be noted that, although the kittens in the 5x group were exposed to 5.57x the recommended dose of flumethrin, they were exposed to only 3.13x the recommended dose of imidacloprid, based on the chemical analyses of the worn collars. Additional study deficiencies are listed under III.C. Deficiencies in this review.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## **I. MATERIALS AND METHODS**

### **A. MATERIALS:**

**Ex. 4 CBI**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# **Ex. 4 CBI**



# **Ex. 4 CBI**

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# **Ex. 4 CBI**

# **Ex. 4 CBI**

# Ex. 4 CBI

## III. DISCUSSION AND CONCLUSIONS

- A. INVESTIGATORS' CONCLUSIONS:** The study author concluded that no adverse treatment-related findings or clinical effects were observed in male or female kittens treated continuously, for 180 days, either with zero, one, three or five PNR 1427 collars or with five placebo collars.
- B. REVIEWER COMMENTS:** A proposed study protocol (MRID 47776801) was reviewed by the Registration Division, OPP, in a Memorandum dated August 28, 2009 (Decision No. 415124). The Agency agreed that three males and three females in the negative and placebo control groups, as opposed to six males and six females per group recommended by the OPPTS 870.7200 Guideline, were sufficient.

Based on chemical analyses of the worn collars, kittens in the 3x and 5x groups were exposed to 3.59x and 3.13x the imidacloprid exposure, respectively, received by kittens that wore one end-use collar. The kittens in the 3x and 5x groups were exposed to 5.09x and 5.57x the flumethrin exposure, respectively, received by kittens that wore one end-use collar. The comparatively low exposures of the 5x group may be due to a problem with the analytical method, a manufacturing problem, or a problem with the study design.

All animals survived to the end of the study. Clinical observations reported included mild signs of abnormal feces (loose stool and/or diarrhea), emesis and ocular discharge in all treatment groups; however, no raw or summarized data were included in the final report. No effects on absolute body weight, food consumption or clinical pathology parameters were observed. Statistically significant findings for hematology and clinical chemistry parameters were not considered treatment-related since they were either isolated, inconsistent or not associated with clinical signs. Body weight gain over the course of the study (days -1 to 180) was decreased 17% in the 5x group females, as compared to the placebo control group. These are considered treatment-related, although similar changes were not seen in the kittens of the 3x group, who may have received very similar exposures.

It is concluded that the margin of safety in kittens exposed to PNR 1427 [imidacloprid (10% w/w) + flumethrin (4.5% w/w)] insecticide collar for 180 days is 3x the recommended dose based on decreased body weight gain over the course of the study (days -1 to 180) in females at 5x the recommended dose. In addition, the exposure from the 5x treatment was 5.57x the recommended dose of flumethrin but only 3.13x the recommended dose of imidacloprid, based on the chemical analyses of the worn collars. The average collar dosage rate for 1X kittens on Day 0 was 9.387 g, equivalent to 4.15 g/kg body weight.

**C. STUDY DEFICIENCIES:**

# Ex. 4 CBI

The deficiencies indicated above are considered to be minor, and do not affect the acceptable classification of this study.

**DATA EVALUATION RECORD**

**CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427, IMIDACLOPRID (10%, W/W) + FLUMETHRIN (4.5%, W/W) COLLAR]**

**STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- PUPPIES;  
NON-GUIDELINE  
MRID 48240112**

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
Arlington, VA 22202

Prepared by  
Summitec Corporation  
9724 Kingston Pike, Suite 602  
Knoxville, Tennessee 37922

Task Order No. 3-C-04

Primary Reviewer:

Donna L. Fefee, D.V.M.

Signature:

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SEP 27 2011

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Thomas C. Marshall, Ph.D., D.A.B.T.

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Robert H. Ross, M.S., Group Leader

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Robert H. Ross

SEP 27 2011

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Angie Edmonds, B.S.

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SEP 27 2011

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EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M.  
Technical Review Branch, Registration Division (7505P)

Signature: M. Hashim  
Date: 1-31-12

Template version 02/06

**DATA EVALUATION RECORD**

**STUDY TYPE:** Companion Animal Safety Study - Puppies; Non-guideline.

**PC CODES:** 129099 (Imidacloprid), 036007 (Flumethrin)

**DP BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collar (10.18% Imidacloprid and 4.47% Flumethrin; Lot No. KP05KTJ)

**SYNONYMS:** M915 Insecticide Animal Collar (small collar)

**CITATIONS:** Madsen, T. (2010) Safety of PNR1427 with reflectors in puppies. Sinclair Research Center, LLC (SRC), Auxvasse, Missouri. Study Number S10064, August 30, 2010. MRID 48240112. Unpublished.

**SPONSOR:** Bayer HealthCare LLC, Animal Health Division, 12809 Shawnee Mission Parkway, Shawnee Mission, Kansas.

**EXECUTIVE SUMMARY:** In a 30-day non-guideline companion animal safety study (MRID 48240112), two groups of three 9-week-old beagle puppies were treated with single PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars either without (Group I, one male and two females) or with (Group II, two males and one female) attached polyamide (Grilamid® TR90) reflectors. Animals were treated on day 0 and observed for 30 days, and the weights of the collars applied on day 0 and the final collar weights (on day 30) were recorded.

There were no treatment-related effects on mortality, systemic or local clinical signs, body weight, cumulative body weight gain, or food consumption.

The percentage of collar weight lost from the collars without reflectors ranged from 6.713% to 10.663% and averaged 9.056%. The percentage of collar weight lost from the collars with attached reflectors (excluding the weight of the reflectors) ranged from 7.159% to 9.028% and averaged 7.861%.

It is concluded that, under the conditions used in this study, the attachment of three polyamide (Grilamid® TR90) reflectors to PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars worn by 9-week-old, 3.077- to 4.951-kg beagle puppies for thirty days was not associated with increased wear on the collars and did not result in a decrease in safety (or increase in toxicological hazard). The percentage weight loss from the collars with the reflectors was 13.2% lower than from collars without the reflectors.

This companion animal safety study in dogs is **Acceptable/Non-guideline**. It does not satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in puppies but does provide scientifically valid information.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## **I. MATERIALS AND METHODS**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# Ex. 4 CBI

## III. DISCUSSION and CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that there were no major adverse treatment-related effects seen in male or female puppies wearing one PNR1427 collar, with or without three attached reflectors, for 30 consecutive days and that the collars were well tolerated and determined to be safe. The study author also concluded that the presence of the reflectors did not cause any increase in the net weight loss from the collars, but actually resulted in an average 13.2% decrease in the net weight loss from the collars during the 30-day exposure period.
- B. **REVIEWER COMMENTS:** The reviewer agrees that no adverse effects were seen. However, it must be noted that the small group size and measuring body weight only at the beginning and end of the 30-day treatment-interval limit the study's sensitivity for detecting a transient effect on body weight. The reviewer also agrees that the percentage of weight lost from the collars with the reflectors was 13.2% lower than the percentage of weight lost from the collars without the reflectors. It is unknown to the reviewer whether a 13.2% lower percentage weight loss would sufficiently decrease exposure to the two active ingredients enough to compromise efficacy. As

the range of percentages lost from the collars without reflectors bracketed the range of percentages lost from the collars with reflectors (6.713%-10.663%, without reflectors, vs. 7.159%-9.028%, with reflectors), it is possible that a study done using a larger sample size would find a smaller difference between the two groups.

**It is concluded that, under the conditions used in this study, the attachment of three polyamide (Grilamid® TR90) reflectors to PNR 1427 [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)] Collars worn by 9-week-old, 3.077- to 4.951-kg beagle puppies for thirty days was not associated with increased wear on the collars and did not result in a decrease in safety (or increase in toxicological hazard). The percentage weight loss from the collars with the reflectors was 13.2% lower than from collars without the reflectors.**

- C. STUDY DEFICIENCIES:** The stated study objective was to evaluate the general safety of PNR1427 with reflectors in puppies. In addition to comparison of collars with reflectors to those without reflectors rather than testing for an adequate (5X) margin of safety, the study design deviates from OPPTS 870.7200 with respect to the following:

## **Ex. 4 CBI**

It was stated that the study design was based on recommendations provided to the sponsor by the EPA during a study design teleconference (June 6, 2009), and on email correspondence between the sponsor and EPA (March 26 and 30, 2010). No documentation of these communications was provided to the reviewer, but, assuming the study design was fully in accordance with EPA recommendations, the above-listed deviations from OPPTS 870.7200 do not impact the study classification.

DATA EVALUATION RECORD

CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427 INSECTICIDE COLLAR]

STUDY TYPE: COMPANION ANIMAL SAFETY - KITTENS (NON-GUIDELINE)

MRIDs 48240113

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
Arlington, VA 22202

Prepared by  
Summitec Corporation  
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Knoxville, Tennessee 37922

Task Order No. 3-C-04

Primary Reviewer:

Virginia A. Dobozy, V.M.D., M.P.H.

Signature:

Virginia A. Dobozy, AE

Date:

SEP 27 2011

Secondary Reviewer:

Thomas C. Marshall, Ph.D., D.A.B.T.

Signature:

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Robert Ross, M.S., Program Manager

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Quality Assurance:

Angie Edmonds, B.S.

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EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M  
Technical Review Branch, Registration Division (7505P)

Signature: M. Hashim  
Date: 1-31-12

Template version 02/06

### DATA EVALUATION RECORD

**STUDY TYPE:** Companion Animal Safety Study - Kittens; Non-Guideline

**PC CODES:** 129099 (Imidacloprid), 036007 (Flumethrin)

**BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR 1427 Insecticide Collar [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)]

**TRADE NAME:** Not provided

**CITATIONS:** Madsen, T.J. (2010) Safety of PNR 1427 with reflectors in kittens. Sinclair Research Center, LLC, Auxvasse, MO. In-Life Testing Facility No. S10605, August 30, 2010. MRID 48240113. Unpublished.

**SPONSOR:** Bayer HealthCare LLC/Animal Health Division, Shawnee Mission, KS

**EXECUTIVE SUMMARY:** In a non-guideline companion animal safety study (MRID 48240113), the influence of reflectors on the net weight loss of PNR 1427 insecticide collars (10% imidacloprid + 4.5% flumethrin) was tested in short hair kittens. One group of one male and two female kittens wore a single end-use collar for 30 days. The other group of two male and one female kittens wore a single end-use collar with three affixed polyamide reflectors. The kittens were observed for systemic and/or local reactions, body weight and food consumption before and after wearing the collar. The weights of the collars pre- and post-treatment were compared.

All animals survived to the end of the study. No systemic or local signs of reactions were observed. Food consumption was comparable between groups and both groups of kittens gained weight over the course of the study.

In Group I, the average collar weight at application was 9.328 g. The average collar dosage based on body weights of kittens in Group I was 8.467g collar/kg body weight, which is equivalent to 846.7 mg imidacloprid + 381.0 mg flumethrin/kg body weight. At the end of the 30-day exposure period, the average weight of the collars removed from kittens in Group I was 8.874 g. The average net loss from the collars in Group I was 0.454 g or 4.874%.

In Group II, the average collar weight (with three reflectors) at application was 10.950g. The average collar dosage calculated based on body weights of kittens in Group II was 7.759g collar/kg body weight, which is equivalent to 775.9 mg imidacloprid + 349.2 mg flumethrin/kg body weight. At the



end of the 30-day exposure period, the average weight of the individual collars removed from kittens in Group II was 10.511 g. The average net loss from the collars was 0.439 g or 4.713%.

Based on the average net collar weight loss of 4.874% from Group I and 4.713% from Group II, the comparative weight loss from the collars with the reflectors was 3.3% lower than from collars without the reflectors.

**The weight loss of PNR 1427 collars with three reflectors was decreased by 3.3% after 30 days of wear in adult cats as compared to collars without reflectors, indicating no decrease in safety (or increase in toxicological hazard) associated with the reflectors.**

This non-guideline companion animal safety study in male and female kittens is acceptable for its intended purpose as a measure of the effect of reflectors on the loss of active ingredients from PNR 1427 (10% imidacloprid + 4.5% flumethrin) collars.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## **I. MATERIALS AND METHODS**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# **Ex. 4 CBI**

# Ex. 4 CBI

## III. DISCUSSION AND CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that the three reflectors affixed to each collar did not increase the net weight loss by the collars and therefore did not increase the release of the two active ingredients as compared to the average net weight loss from a single collar without reflectors. Instead, the presence of the reflectors on the collar resulted in 3.3% decrease in the net collar weight loss as compared to the net weight loss from the collars without reflectors during the 30-day exposure period.
- B. **REVIEWER COMMENTS:** All animals survived to the end of the study. No systemic or local signs of reactions were observed. Food consumption and weight gain was comparable between the two groups of kittens.

In Group I, the average collar weight at application was 9.328 g. The average collar dosage based on body weights of kittens in Group I was 8.467g collar/kg body weight, which is equivalent to 846.7 mg imidacloprid + 381.0 mg flumethrin/kg body weight. At the end of the 30-day exposure period, the average weight of the collars removed from kittens in Group I was 8.874 g. The average net loss from the collars in Group I was 0.454 g. The average net collar weight loss was 4.874%.

In Group II, the average collar weight (with three reflectors) at application was 10.950g. The average collar dosage calculated based on body weights of kittens in Group II was 7.759g collar/kg body weight, which is equivalent to 775.9 mg imidacloprid + 349.2 mg flumethrin/kg body weight. At the end of the 30-day exposure period, the average weight of the individual collars removed from kittens in Group II was 10.511 g. The average net loss from the collars was 0.439 g. The average net collar 4.713%.

Based on the average net collar weight loss of 4.874% from Group I and 4.713% from Group II, the comparative weight loss from the collars with the reflectors was 3.3% lower than from collars without the reflectors.

**The weight loss of PNR 1427 collars with three reflectors was decreased by 3.3% after 30 days of wear in adult cats as compared to collars without reflectors, indicating no decrease in safety (or increase in toxicological hazard) associated with the reflectors.**

**C. STUDY DEFICIENCIES:**

Only three animals per group were included in the study. The Companion Animal Safety Guideline (CAS) (OPPTS 870.7200) requires six animals/sex/group. However, according to the study protocol, the study design was agreed to during teleconferences (June 6, 2009) and email correspondence (March 16 & 30, 2010) between the sponsor and the EPA. In addition, this study is not considered a CAS guideline study.

DATA EVALUATION RECORD

CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427 INSECTICIDE COLLAR]

STUDY TYPE: COMPANION ANIMAL SAFETY - CATS (NON-GUIDELINE)

MRIDs 48240114

Prepared for  
Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 South Crystal Drive  
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Prepared by  
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9724 Kingston Pike, Suite 602  
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Task Order No. 3-C-04

Primary Reviewer:

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Signature:

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SEP 27 2011

Secondary Reviewer:

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Thomas C. Marshall, AE  
SEP 27 2011

Robert Ross, M.S., Program Manager

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Robert H. Ross  
SEP 27 2011

Quality Assurance:

Angie Edmonds, B.S.

Signature:

Date:

Angie Edmonds  
SEP 27 2011

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EPA Primary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Jan. 27, 2012

EPA Secondary Reviewer: Masih Hashim, Ph.D., D.V.M  
Technical Review Branch, Registration Division (7505P)

Signature: M Hashim  
Date: 1-31-12

Template version 02/06

**DATA EVALUATION RECORD**

**STUDY TYPE:** Companion Animal Safety Study - Cats – Non-Guideline

**PC CODES:** 129099 (Imidacloprid), 036007 (Flumethrin)

**BARCODE:** 385560

**TEST MATERIAL (PURITY):** PNR 1427 Insecticide Collar [Imidacloprid (10% w/w) and Flumethrin (4.5% w/w)]

**TRADE NAME:** Not provided

**CITATIONS:** Delport, P.C. (2010) Target animal safety with PNR 1427 collar with and without reflectors when applied once to adult cats. ClinVet International (Pty) Ltd, Bloemfontein, Republic of South Africa. Lab Study No. CV 09/676, May 18, 2010. MRID 48240114. Unpublished.

**SPONSOR:** Bayer HealthCare LLC/Animal Health Division, Shawnee Mission, KS

**EXECUTIVE SUMMARY:** In a non-guideline companion animal safety study (MRID 48240114), the influence of reflectors on the net weight loss of PNR 1427 insecticide collars (10% imidacloprid + 4.5% flumethrin) was tested in adult short hair cats. One group of four males and four females wore a single collar for 30 days. The other group of four males and four females wore a collar with three affixed polyamide reflectors. The cats were observed for systemic and/or local reactions and body weight before and after wearing the collar. The weights of the collars pre- and post-treatment were compared.

All animals survived to the end of the study. No systemic or local signs of reactions were observed. The cats maintained their body weight over the course of the study.

For the cats wearing the collars without reflectors, the calculated average weight of the collars before application was 10.149 g and upon removal on day 30, it was 9.748 g. The calculated average net weight loss of the collars was 0.401 g, which is equivalent to 3.951% of the collar weight before application.

For the cats wearing collars with the reflectors, the calculated average weight of the collars was 12.064 g and upon removal on day 30, it was 11.688 g. The calculated average weight loss of the collars was 0.378 g, which is equivalent to 3.622% of the collar weight before affixing the three reflectors and before application.

**The weight loss of PNR 1427 collars with three reflectors was decreased by 8.33% after 30 days of wear in adult cats as compared to collars without reflectors.**

This non-guideline companion animal safety study in male and female adult cats is acceptable for its intended purpose as a measure of the effect of reflectors on the loss of active ingredients from the PNR 1427 (10% imidacloprid + 4.5% flumethrin) collars.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## **I. MATERIALS AND METHODS**

# **Ex. 4 CBI**



# **Ex. 4 CBI**

# **Ex. 4 CBI**

# Ex. 4 CBI

## III. DISCUSSION AND CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that the three reflectors affixed on to each collar did not increase the net weight loss by the collars and therefore did not increase the release of the two active ingredients as compared to the collars without the reflectors.
- B. **REVIEWER COMMENTS:** All animals survived to the end of the study. No systemic or local signs of reactions were observed. The cats maintained their body weight over the course of the study.

For the cats wearing the collars without reflectors, the calculated average weight of the collars before application was 10.149 g and upon removal on day 30, it was 9.748 g. The calculated average net weight loss of the collars was 0.401 g, which is equivalent to 3.951% of the collar weight before application.

For the cats wearing collars with the reflectors, the calculated average weight of the collars was 12.064 g and upon removal on day 30, it was 11.686 g. The calculated average weight loss of the collars was 0.378 g, which is equivalent to 3.622% of the collar weight before affixing the three reflectors and before application.

**The weight loss of PNR 1427 collars with three reflectors was decreased by 8.33% after 30 days of wear in adult cats as compared to collars without reflectors.**

C. **STUDY DEFICIENCIES:**

No raw data or summary tables were provided for the clinical observations results.

**DATA EVALUATION RECORD**

**CYCLOPROPANECARBOXYLIC ACID, 3-(4-CHLOROPHENYL)  
[PNR 1427, IMIDACLOPRID (10%, W/W) + FLUMETHRIN (4.5%, W/W) COLLAR]**

**STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- ADULT DOGS;  
NON-GUIDELINE  
MRID 48240115**

Prepared for  
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**Disclaimer**

This review may have been altered subsequent to the contractor's signatures above.

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**DATA EVALUATION RECORD**

**STUDY TYPE:** Companion Animal Safety Study - Adult Dogs; Non-guideline.

**PC CODE:** 129099 (Imidacloprid), 036007 (Flumethrin)

**DP BARCODE:** 385560

**TEST MATERIAL (PURITY):** IMI/FLU 10/4,5 Collar (9.9% Imidacloprid and 4.5% Flumethrin; Lot No. KP05KGL)

**CITATIONS:** Bach, T. (2010) Target animal safety with a 10% imidacloprid + 4.5% flumethrin collar with or without reflector clips applied once to adult dogs. Bayer Animal Health GmbH, Research and Development, Clinical Research and Development - Animal Centre, Monheim, Germany. Study Number 35637, April 27, 2010. MRID 48240115. Unpublished.

**SPONSOR:** Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee Mission, Kansas.

**EXECUTIVE SUMMARY:** In an 30-day non-guideline companion animal safety study (MRID 48240115), two groups of four male and four female adult beagle dogs were treated with single IMI/FLU 10/4,5 Collars (9.9% Imidacloprid and 4.5% Flumethrin; Lot #KP05KGL), either without (Group 1) or with (Group 2) attached polyamide (Grilamid® TR90) reflectors. Animals were treated on day 0 and observed for 30 days, and the weights of the collars applied on day 0 and the final collar weights (on day 30) were recorded.

There were no treatment-related effects on mortality, systemic clinical signs, body weight, or cumulative body weight gain. Local effects included a 1-cm<sup>2</sup> area with broken hair on the ventral neck of one Group 1 animal on days 25-29, which was noted to be partially hairless on day 30, an approximately 3 cm by 0.5 cm area on the dorsal neck with broken hair, hairlessness, and erythema on the same animal at an unspecified time, and areas of broken hair on the ventral neck area (measuring less than 1 cm<sup>2</sup>) on a different Group 1 animal and two Group 2 animals on day 30.

The percentage of collar weight lost from the collars without reflectors ranged from 2.447% to 4.754% and averaged 3.225%. The percentage of collar weight lost from the collars with attached reflectors (excluding the weight of the reflectors) ranged from 2.224% to 4.263% and averaged 3.114%.

It is concluded that, under the conditions used in this study, the attachment of three polyamide (Grilamid® TR90) reflectors to IMI/FLU 10/4,5 Collars worn by adult, 8.7- to 11.7-kg beagle dogs for thirty days does not appreciably decrease safety. The percentage of weight loss from the collars with the reflectors was 3.4% lower than from collars without the reflectors.

This companion animal safety study in dogs is **Acceptable/Non-guideline**. It does not satisfy the guideline requirement for a companion animal safety study (OPPTS 870.7200) in adult dogs but does provide scientifically valid information.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## **I. MATERIALS AND METHODS**

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## III. DISCUSSION and CONCLUSIONS

- A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that IMI/FLU 10/4,5 Collars, with or without three attached reflectors, were well tolerated when worn by adult dogs for 30 consecutive days, and that the treatment-related local signs, such as thinning of the hair and skin irritation, were due to mechanical rubbing of the collars against the skin rather than toxicity of the active ingredients. The study author also concluded that the presence of the reflectors did not cause any increase in the net weight loss from the collars, and therefore did not result in increased release of the active ingredients from the collars.
- B. **REVIEWER COMMENTS:** The reviewer agrees that no adverse effects were seen. However, it must be noted that measuring body weight only at the beginning and end of the 30-day treatment-interval and omission of food consumption measurements limit the study's sensitivity. The reviewer also agrees that the percentage of weight lost from the collars with the reflectors was lower than the percentage of weight lost from the collars without the reflectors. It is unknown to the reviewer whether a 3.4% lower percentage weight loss would sufficiently decrease exposure to the two active ingredients enough to compromise efficacy.

It is concluded that, under the conditions used in this study, the attachment of three polyamide (Grilamid® TR90) reflectors to IMI/FLU 10/4,5 Collars worn by adult, 8.7- to 11.7-kg beagle dogs for thirty days does not appreciably decrease safety. The percentage of weight loss from the collars with the reflectors was 3.4% lower than from collars without the reflectors.

- C. **STUDY DEFICIENCIES:** In addition to comparison of collars with reflectors to those without reflectors rather than testing for an adequate (5X) margin of safety, the study design deviates from OPPTS 870.7200 with respect to the following:
- No raw data or summary tables were provided for the clinical observation data.

# Ex. 4 CBI

However, only the first deviation is considered to be a deficiency. The stated study objective was to evaluate the local tolerance of a collar containing 10% imidacloprid plus 4.5% flumethrin when worn by adult dogs with or without reflectors and to investigate whether the reflector clips influence the net weight loss from the collar during use, as a measure of the amount of active ingredients released. The latter modifications to the OPPTS 870.7200 protocol do not compromise the investigators' ability to reach the stated objective.

1. **DP BARCODES:** 385560, 396978
2. **PC CODES:** 129099 (Imidacloprid); 036007 (Flumethrin)
3. **CURRENT DATE:** January 26, 2012
4. **TEST MATERIAL:** PNR 1427 insecticide collar (10.0% Imidacloprid and 4.5% Flumethrin)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Companion Animal Safety Study/Adult Cats  Sinclair Research Center, MO  Study No. S10065/April 1, 2010 (+2 amendments dated June 2, 2010 & November 22, 2011)	48240108 48674702	61-day study: One group of 3M & 3F adult cats served as negative controls; one group of 3M & 3F were in the placebo control group and wore 5 end-use collars minus the active ingredients continuously for 61 days. A third group of 3M & 3F wore one end-use collar continuously for 61 days. In a fourth group of 6M & 6F, five end-use collars were applied on day 0 and were replaced by new collars on days 14, 28 and 42. The end-use collars worn by selected cats in the 1x and 5x groups were analyzed post-removal to determine the exposures of these cats to the active ingredients. No effects were observed. Based on the chemical analyses of worn collars and information reported in MRID 48674702, cats in the 5x group were exposed to 5.2x the recommended dose of imidacloprid and 4.0x the recommended dose of flumethrin. The mean collar weight (after trimming) applied to the 1x cats was 11.17 g equivalent to 2.82 g/kg body weight.	N/A	A (guide- line)
Companion Animal Safety Study/Adult Dogs  Sinclair Research Center, MO  Study No. S10064/April 23, 2010 (+1 amendment dated November 22, 2011)	48240109 48674701	61-day study: One group of 3M & 3F adult dogs served as negative controls; one group of 3M & 3F were in the placebo control group and wore 5 end-use collars minus the active ingredients continuously for 61 days. A third group of 3M & 3F wore one end-use collar continuously for 61 days. In a fourth group of 6M & 6F, five end-use collars were applied on day 0 and were replaced by new collars on days 14, 28 and 42. No effects were observed except for erythema and/or hair loss on the throat or neck. Based on the chemical analyses of worn collars and information reported in MRID 48674701, dogs in the 5x group were exposed to 10.88x the imidacloprid and 4.05x the flumethrin that dogs in the 1x group were exposed to. The mean collar weight (after trimming) applied to the 1x dogs was 37.93 g or 3.22 g/kg b.w.		A (guide- line)

<p>Companion Animal Safety Study/Puppies (7 weeks old on day 0)</p> <p>Sinclair Research Center, MO</p> <p>Study No. S10062/June 16, 2010</p>	<p>48240110</p>	<p>180-day study: Groups of 6M &amp; 6F beagle puppies (7 weeks old on Day 0) were treated at 1x (1 collar), 3x (3 collars), and 5x (5 collars). Two additional groups of 3M &amp; 3F were untreated or were treated with 5 placebo (no active ingredient) collars. For the 5x group initial collars were placed on the animals on day 0, and the puppies were retreated (existing collars replaced with new collars) on days 29, 90, 125 and 148). There were no treatment-related effects on mortality, absolute body weight, food consumption, hematology or clinical chemistry. The 5x females had a transient decrease in body weight gain (25% less than controls from day -1 to 17). Mildly increased creatinine kinase activity in 3x and 5x animals (349, 940, 1074 U/L for negative controls, 3x and 5x, respectively). There were local findings such as erythema, hair loss or thinning of hair, bruising, abrasions or scabbing that were presumably due to the mechanical trauma of wearing one or more collars.</p> <p>Based on collar weight losses and chemical analyses of worn collars, the imidacloprid exposure of puppies in the 3x and 5x groups was 3.02x and 4.89x that of the 1x group, and the flumethrin exposure of puppies in the 3x and 5x groups was 2.46x and 1.45x that of the dogs in the 1x group.</p> <p>Based on transient decreased body weight gain in 5x females, it is concluded that the margin of safety in 7-week-old 1.53-2.96 kg beagle puppies treated with PNR collars is 3x the recommended dose of one collar per puppy. The average collar dosage rate for 1x animals on day 0 was 10.156 g, equivalent to 5.096 g/kg b.w.</p>		<p>A (guide- line)</p>
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<p>Companion Animal Safety Study/Kittens (68-71 days old on day 0)</p> <p>Sinclair Research Center, MO</p> <p>Study No. S10063/June 16, 2010</p>	48240111	<p>180 day study: Groups of 6M &amp; 6F kittens (68-71 days old on day 0) were treated at 1x (1 collar), 3x (3 collars), and 5x (5 collars). Two additional groups of 3M &amp; 3F were untreated or were treated with 5 placebo (no active ingredient) collars. For the 1x, 3x and 5x groups the kittens were retreated (existing collars taken off and replaced with new collars) on days 29, 90 and 149. End-use collars worn by selected kittens in the 1x, 3x and 5x groups were analyzed after removal to determine exposures to the active ingredients. All kittens survived to the end of the study; there were no effects except body weight gain over the course of the study (days -1 to 180) was decreased 17% in the 5x group females as compared to the placebo control group.</p> <p>Based on chemical analyses of the worn collars kittens in the 3x and 5x groups were exposed to 3.59x and 3.13x the imidacloprid that kittens in the 1x group were exposed to. Kittens in the 3x and 5x groups were exposed to 5.09x and 5.59x the flumethrin that kittens in the 1x group were exposed to.</p> <p>It is concluded that the margin of safety in kittens exposed to the PNR 1427 collar is 3x, based on decreased body weight gain over the 180 day study in 5x females. The average collar dosage rate for 1x kittens on day 0 was 9.387 g, equivalent to 4.15 g/kg.</p>		A (guide-line)
<p>Companion Animal Safety Study (non-Guideline)/Puppies</p> <p>Sinclair Research Center, MO</p> <p>Study No. S10064/August 30, 2010</p>	48240112	<p>30-day non-guideline study: 2 groups of 3 9-week-old beagle puppies were treated with single PNR 1427 collars, either without (Group 1, 1M &amp; 2F) or with (Group 2 (2M &amp; 1F) attached polyamide reflectors. There were no treatment-related effects on mortality, systemic or local clinical signs, body weight, cumulative weight gain or food consumption.</p> <p>The percentage of collar weight lost from collars without reflectors ranged from 6.713% to 10.663% averaging 9.056%; percentage of collar weight lost from collars with reflectors (excluding weight of reflectors) ranged from 7.159% to 9.028% and averaged 7.861%.</p> <p>Conclusion: attachment of 3 polyamide reflectors was not associated with increased wear or the collars and did not result in an decrease in safety (or increase in toxicological hazard). Percentage weight loss from collars with the reflectors was 13.2% lower than from collars without the reflectors.</p>		A (non-guide-line)

Companion Animal Safety Study (non-Guideline)/Kittens  Sinclair Research Center, MO  Study No. S10605/August 30, 2010	48240113	30 day study: Group I (1M and 2F) wore a single collar without a reflector; Group II (2M & 1F) wore a single collar with attached 3 polyamide reflectors. No systemic or local reactions were seen  Based on the average collar weight loss of 4.874% from Group I and 4.713% from Group II, the comparative weight loss from the collars with reflectors was 3.3% lower than from collars without reflectors.		A (non-Guideline)
Companion Animal Safety Study (non-Guideline)/Adult Cats  ClinVet International Ltd, Bloemfontein, South Africa  Study No. CV/09/676 / May 18, 2010	48240114	30 day study: Group I (4M & 4F) wore a single collar without a reflector; Group II (4M & 4F) wore a collar with 3 attached polyamide reflectors. No systemic or local reactions were seen.  Based on the average collar weight loss of 3.951% in Group I and 3.622% in Group II, the weight loss of the collars with 3 reflectors was decreased by 8.33%.		A (non-Guideline)
Companion Animal Safety Study (non-Guideline)/Adult Dogs  Bayer Animal Health GmbH Research & Development, Monheim, Germany  Study No. 35637/April 27, 2010	48240115	30 day study: Group I (4M & 4F beagles) wore a single collar without reflectors; Group II (4M & 4F) wore a collar with 3 attached polyamide reflectors. No indications of systemic effects. Local effects (seen in 2 Group I and 2 Group II dogs) included partial hairlessness on neck with erythema, and "broken hair on the ventral neck area."  Percentage of collar weight loss was 3.225% (range: 2.447-4.754%) in Group I and 3.114% (range: 2.224-4.263%) in Group II. The percentage weight loss from the collars with reflectors was 3.4% lower than from collars without the reflectors.		A (non-Guideline)

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived